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COMPLETE SPECIFICATION

Improvements in or relating to Adhesive Preparations for Medical and like Use and Methods of Obtaining the Same

We, THE NATIONAL JEWISH HOSPITAL AT DENVER, a Corporation organized under the Laws of the State of Colorado, one of the United States of America, of 3800 Colfax Avenue, City of Denver, State of Colorado, United States of America, Assignees of HARRY JOHN COPPER, a Citizen of the United States of America, of 1295 Clermont Street, City of Denver, State of Colorado, United States of America, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

The invention relates to adhesives and to transparent dried films thereof. More particularly, the invention relates to a skin adhesive and to transparent dried films thereof containing an agent which can act transdermally on human skin for the production of medical, therapeutic, diagnostic and biological effects. The invention also relates to such adhesives which are capable of being spread, sprayed or painted onto the surface of the skin and which quickly dry to form flexible, but adherent, transparent films which do not hermetically seal the active agent within the body of the film, but which gradually release it under the influence of the normal moisture and insensible perspiration of the skin, while at the same time allowing the skin to "breathe" sufficiently to prevent skin maceration and reddening, with consequent masking of the true results based upon the active agent itself.

In the past, various means have been employed to bring medicaments and the like into contact with the skin. For example, various vehicles such as salves, pastes, ointments, varnishes, adhesive tapes and the like have been used in order to apply antiseptics and germicides to the skin for the purpose of keeping the surface of the skin sterile and free from microorganisms. However, employment of the prior combinations has in general been accompanied by many drawbacks. The known preparations have only exercised a superficial action and the active agent has not penetrated through the skin to an extent permitting it to exercise a deeper and more reliable action on the human body.

It has been proposed to form a diagnostic composition comprising tuberculin and a water permeable adhesive, which may be a water-soluble cellulose derivative. It has also been proposed to prepare surgical dressings comprising as essential ingredients a water-soluble cellulose derivative, a plasticiser therefor and a bacteriostatic sulphonamide.

Among the objections to the prior preparations are the use therein of antiseptic or like agents active at the surface of the skin but not transdermally active, use of a vehicle which imprisons the active agent within it and only permits utilization of the relatively very small amount present at the point where the film or patch directly contacts the skin, use of a vehicle which does not leave a transparent film on the skin that will permit the condition of the latter to be observed at all times, use of a combination which does not allow the insensible perspiration of the body to escape and thereby a macerated, soggy, moist and reddened condition of the skin results, even when no diagnostic or like agent is present, use of vehicles for active agent which irritate the skin and have a deleterious and undesirable action separate from that of the active agent incorporated into the vehicle, use of a combination which does not dry quickly or which is easily removed, either mechanically or by action of water, use of a combination which when dried upon the skin is brittle or without the necessary flexibility, use of a vehicle which reacts with or destroys the active agent, use of a vehicle which neither keeps the active agent in suspen-

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sion nor allows of ready resuspension of active agent which has settled out or packed down hard in the bottom of a container for the same, and use of a solvent for the combination which contains water or which is not perfectly dry or which takes up moisture too rapidly from the atmosphere upon standing.

The above mentioned objections to prior products indicate the exacting requirements for a satisfactory skin adhesive useful for its medical, therapeutic, diagnostic and biological effects, especially when the active agent being used is a transdermally active substance which must not only contact the surface of the skin but must also be continuously kept in contact therewith and caused to penetrate therethrough in substantial amounts.

We have found that the objections above referred to are overcome and that commercially useful, as well as clinically satisfactory, adhesive preparations and films may be obtained in accordance with our invention by utilizing a non-aqueous dry combination of a highly hygroscopic active agent suspended in a solution of a water insoluble but water permeable cellulose ether in a volatile water immissible inert organic solvent. The preferred adhesive preparations are those wherein the active agent is effective transdermally on human or animal skin, wherein also the cellulose ether is a water insoluble lower alkyl ether of cellulose which is pervious to water and wherein the suspending liquid has a specific gravity approximately the same as the active agent.

The following examples will serve to illustrate the invention.

EXAMPLE 1.

5 grams of ethyl cellulose, having a medium ethoxy content (45 to 46.5%) and a viscosity of approximately 100 centipoises in toluene-ethanol solvent (60:40), are stirred and dissolved in enough of a mixture of 8 volumes of dry carbon tetrachloride and 2 volumes of dry chloroform to give 100 cc. of adhesive solution. 20 grams of dry, powdered and highly hygroscopic "autolytic" tuberculin, prepared for example as described in our copending application for Patent No. 632,672, are then stirred uniformly into the solution of ethyl cellulose in carbon tetrachloride-chloroform. A uniform suspension is thus obtained. It is non-inflammable and the suspending adhesive liquid has just the right specific gravity (approximately 1.57 20°/4°) to keep the tuberculin uniformly suspended so that it does not separate out either at the surface of the liquid or at the bottom of the container. Moreover, the solvent in this preparation is sufficiently volatile to evaporate fairly rapidly (in a few minutes) in contact with the skin of the living body to give an adherent uniform, clear, transparent, flexible dry film without boiling or forming bubbles in the film or producing opacity thereof due to too rapid evaporation. The final liquid preparation of this example also has the correct viscosity to make it easy to collect an appreciable amount on a glass rod or tooth pick or like simple applicator and apply in one or two strokes as a uniform thin film or patch on the skin. It is more viscous than water but will readily pour from a container and is a thinner liquid than molasses.

The dry films of this example, which form when the liquid is spread over the skin, are adherent, yet flexible, and clearly transparent so that the color and condition of the skin underneath can be readily observed at all times. Furthermore, the dry films of this example, although water insoluble, are nevertheless pervious to water to the extent that perspiration does not accumulate under them and cause a macerated and reddened condition of the skin which would interfere with reliable testing or diagnosis. This feature of perviousness to water and moisture is important because it permits the highly hygroscopic autolytic tuberculin incorporated into the film to take up moisture from the skin and feed its way down through the body of the film into direct contact with the skin.

The tuberculin present in the dry films of this example is especially valuable when testing for tuberculous subjects because it is transdermally highly active and can be used in excess without danger because it is only taken up by the skin to the extent necessary to elicit a skin reaction or reddened and perhaps edematous condition of the skin. It has the advantage of keeping indefinitely in a water-free solvent and it does not produce untoward focal or general reactions, nor does permanent scarring occur at the local site of reaction.

EXAMPLE 2.

25 grams of "standard" ethyl cellulose having an ethoxy content of 48.5 to 49.5% and a viscosity in 5% solution of toluene-ethanol solvent (80:20) of 200 centipoises, are dissolved in enough of a mixture of 5 volumes of tetrachloroethylene and 5 volumes of chloroform to give 500 cc. of adhesive solution. 100 grams of dry powdered and highly hygroscopic "autolytic" tuberculin, prepared for example as described in our copending Application for Patent No.

632,672, are stirred into the solution. The uniform suspension thus obtained has properties similar to that of Example 1 and is a commercially and clinically valuable preparation.

EXAMPLE 3.

25 grams of ethyl cellulose, having an ethoxyl content of 46% and a viscosity of 100 centipoises in a 5% solution in toluene-ethanol (80:20), are dissolved in 1 liter of chemically pure chloroform. About ½ hour is needed to dissolve all of the ethyl cellulose, if stirring is used from time to time. 100 grams of dry "autolytic" tuberculin powder prepared for example as described in our copending Application for Patent No. 632,672, are added to the chloroform solution while stirring thoroughly. The glass flask containing the resulting suspension is stoppered by a tin-foil coated cork. The adhesive suspension thus obtained is uniform when first made up and is satisfactory for immediate use as a diagnostic testing material to be applied to the skin of subjects to determine if they are tuberculous. However, since chloroform alone is used as a solvent for the ethyl cellulose, it does not have the necessary specific gravity to insure that the suspended tuberculin will not settle out upon storage. Hence, it is desirable to convert the suspension into a more practical form which is permanent and retains its uniformity. For this purpose, we have found that any of our new suspensions, including the chloroform suspension of the present example, may be spread out in the form of thin films on a suitable flat surface, such as a glass plate, and dried while taking care not to cause too rapid removal of solvent and formation of bubbles in the film. We prefer to dry the films under controlled partial vacuum at ordinary room temperature. Before the films are completely dried and while they retain a certain degree of flexibility, they can be cut into any desired shapes and sizes. For example, strips 0.3 by 1.0 centimeter can be cut out on the plate and the individual strips separated from the plate by a thin sharp blade which peels them away from the glass without substantially altering their shape. After the strips are thus separated, the vacuum drying is continued until all of the chloroform is removed. These individual strips constitute a valuable form of test material for diagnosis of tuberculosis. They can be put in dry containers, sealed preferably by paraffin coated stoppers or screw caps, and sold to the trade. They can be stored indefinitely in this form and do not lose their biological activity.

In use, a test strip or two of the dried film measuring 0.3 by 1.0 cm. can be laid upon the skin of the forearm or other site of an individual and a drop of chloroform placed on the strip. The drop of chloroform immediately flattens the strip against the skin, dissolved the ethyl cellulose sufficiently to cause the strip to adhere firmly and then dries to leave an adherent film containing the biologically active "autolytic" tuberculin and which film has a transparency permitting one to readily observe the presence or absence of a positive skin reaction. If a positive reaction occurs, it will appear within 24 or 48 hours, or in some cases earlier, and may persist for a period of 10 days to 2 weeks in many instances. If it is desired to remove the test material at any time it can be done by applying a few drops of chloroform, acetone-alcohol mixture or any other suitable solvent for the ethyl cellulose.

From the above example, it will be apparent that the invention includes dry films as well as the liquid adhesive forms from which the dry films are prepared. Either form is valuable as an article of trade. However, both forms are hygroscopic and the usual precautions against absorption of water during preparation and use should be observed.

EXAMPLE 4.

10 grams of ethyl cellulose, "standard ethoxy" type having an ethoxy content of 48.5 to 49.5% and a viscosity in 5% solution of toluene-ethanol (80:20) of 7 centipoises, are dissolved in enough of a mixture of 4 volumes of carbon tetrachloride and 1 volume of chloroform to give 100 cc. of adhesive solution. 20 grams of dry powdered and highly hygroscopic "autolytic" tuberculin, prepared as described in our copending Application for Patent No. 632,672, are stirred uniformly into the solution. The uniform suspension thus obtained is similar to that of Example 1 and can be used in the same manner. However, it is of somewhat lower viscosity, but still has satisfactory covering power.

In the examples given above the active agent is a tuberculo protein made as described in our copending Application for Patent No. 632,672. It is highly hygroscopic and readily takes up 90% or more of its weight of moisture from the air upon exposure thereto. Wherever in the appended claims we refer to a "hygroscopic transdermally active undenatured tuberculo protein" we wish to be understood as referring to such hygroscopic protein whether made by the exact method described in our Application for Patent

No. 632,672 or by methods giving an equivalent protein product.

Instead of using a tuberculo protein in our preparations, other transdermally biologically active substances and hygroscopic protein preparations may also be used, such for example as many of the well known allergens, particularly those obtained by hydrolytic or autolytic methods from more complex natural substances, which at the same time have the necessary hygroscopicity.

A lower alkyl ether of cellulose, or mixture of such ethers, which are insoluble in water but which nevertheless form dry film permeable to water can be used in the invention. For example, suitable ethyl celluloses which we can use are those wherein the cellulose has been ethylated to the extent of an average of about 2.4 to 2.5 ethoxy groups (—OC_2H_5) per glucose residue of cellulose. Specifically, the ethyl celluloses which can be used are those having an ethoxy (—OC_2H_5) content between about 44% and 50%.

In general, when making the liquid adhesive suspensions of our invention, we use solutions in the organic water immiscible solvent of from 1 to 10% of cellulose ether and preferably about 5%.

Moreover, when making up the liquid adhesive suspensions we incorporate anywhere from 10 to 30% of active agent such as tuberculo protein. Thus, when the liquid preparations are thoroughly dried they contain anywhere from about 50% up to about 95% of active solid hygroscopic substance. In the case of "autolytic" tuberculin prepared by our Specification No. 632,672 we prefer to use about 20% concentration of the same suspended in the liquid adhesive preparation, although percentages anywhere from about 10 to 30% will give good results.

From the above description it is apparent that the dry films of the invention can be made from any of the liquid preparations described merely by careful drying or evaporation.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. The method of producing an adhesive preparation which comprises suspending a hygroscopic transdermally biologically active substance in a solution of a water insoluble but water permeable cellulose ether in a volatile water immiscible inert organic solvent.

2. The method according to Claim 1, wherein the cellulose ether is a lower alkyl ether of cellulose.

3. The method according to Claim 2, wherein the cellulose ether is an ethyl cellulose having an ethoxy content between about 44% and 50%.

4. The method according to any of the preceding claims, wherein the active substance is a dry hygroscopic transdermally active tuberculo protein.

5. The method according to Claim 4, wherein the protein is an undenatured tuberculo protein substantially equivalent to that obtained by growing tubercle bacilli for about one month on non-protein medium, autolyzing the bacilli and separating the water soluble tuberculo protein from the autolyzate.

6. The method according to any of the preceding claims, wherein more than about 10% by weight and less than about 30% by weight of the active substance is suspended in a solution of more than about 1% by weight and less than about 10% by weight of cellulose ether in said organic solvent.

7. The method according to Claim 6, wherein about 20% by weight of a dry hygroscopic transdermally active undenatured tuberculo protein is suspended in a solution of about 5% by weight of water insoluble but water permeable ethyl ether of cellulose in a volatile water immiscible inert organic solvent.

8. The method according to any of the preceding claims wherein the solvent comprises 4 parts of carbon tetrachloride and 1 part of chloroform.

9. The method of preparing a dry film patch test which comprises spreading the adhesive preparation prepared in accordance with any of the preceding claims on a flat surface in the form of thin films and drying.

10. The method according to Claim 9, wherein the films are dried under controlled partial vacuum at room temperature.

11. Adhesive preparations whenever prepared by the method described in any of claims 1 to 8.

12. Dry film patch tests whenever prepared from the adhesive preparations described in any of claims 1 to 8.

13. Dry film patch tests whenever prepared by the method described in claim 9 or 10.

Dated the 16th day of May, 1947.

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